REMARKS

Claims 24-28 are pending in the Subject Application.

TELEPHONE INTERVIEW

Applicants wish to thank Examiner Riggens and Supervisory Examiner Shukla for the telephonic interview of November 18, 2005. In the interview Applicants reiterated their position that the 103 rejection is not proper.

REJECTION UNDER 35 U.S.C. § 103:

In the Office Action, the Examiner rejected claims 24-26 under 35 U.S.C. § 103 as allegedly being unpatentable over Ahrens further in view of Bonadio et al, and Lee et al. The Examiner alleged that claims to use of ex-vivo transduced/transfected mesechymal stem cells expressing BMP-2, for inducing organized functional bone formation at a site of bone infirmity is obvious in view of Bonadio, as allegedly Figure 8 of Bonadio shows organized formation at the rejoin of the break. However, Applicants submit that Figure 8 refers to direct gene transfer experiments for parathyroid hormone gene transfer, and thus do not show organized bone formation, nor suggest organized bone formation, as a result of transfer of ex-vivo cultured MSC's expressing BMP-2.

Applicants maintain that Bonadio does not render the claimed invention obvious. Applicants have provided a Declaration, including references to support that Bonadio does not credibly specifically target progenitor cells using direct gene transfer. Applicants submit that the Examiner has not provided a *prima facie* factual basis for rebutting this contention. Moreover, even, as the Examiner suggests, were Bonadio to succeed in minimal gene transfer

to progenitor cells, this is a minority of the cell types exposed to the vector, whereas Applicants transfer an enriched population of stem cells expressing BMP-2.

Applicants maintain that the experiments conducted with CHO cells expressing BMP-2 are not "apples and oranges", but rather serve as an indication of the contrast between what Bonadio describes and the instant invention. Applicants maintain that the major cell type at a site of bone infirmity taking up a BMP-2 is a differentiated cell, and not a stem or progenitor cell. Thus, engineered CHO cells express BMP-2, much like the bulk of the cells which are exposed to the BMP-2 construct, following gene transfer experiments as described by Bonadio. Bonadio contends, among other things, that progenitor cells are targeted by direct gene transfer. Applicants maintain this is not a credible contention. Applicants maintain that the references provided in the previous response, as well as the Declaration make this point clear. The Examiner has failed to provide any *prima facie* factual basis that Bonadio, via direct gene transfer, successfully **targets** stem cells. Indeed the Examiner agreed that any uptake by such cells, even progenitor cells which are more differentiated than the MSCs, is significantly diminished, in comparison to more differentiated cells, which comprise the majority of cells types at the site of bone infirmity. Thus, the CHO-BMP control serves as a more relevant indicator as to what direct gene transfer produces at a fracture site. Applicants moreover, agree, that expression of BMP-2 from a more differentiated cell type may stimulate "disorganized bone formation" (paragraph 121, Example 11) and in fact the bone formation is short-lived, as 8 weeks after implant, bone resorption is seen in CHO- but not MSC-expressing BMP-2 cells.

In marked contrast, implantation of an enriched MSC population expressing BMP-2 promoted organized bone formation, within the boundaries of the fracture edges, and no bone resorption was observed. These differences could not have been predicted, based on Bonadio, or Ahrens, or Lee, alone or in combination. None of these references would predict, that

transfer of an enriched, MSC population, expressing BMP-2 would specifically produce organized bone formation, at a site of infirmity, nor that only implantation of such a population prevented resorption of the newly formed bone, but rather, its culmination in proper, functional bone.

The Examiner alleged that these findings are not unexpected in view of Bonadio,

"The methods of Bonadio alone teach that organized bone formation is achieved. This is evidenced by Fang (PNAS USA 93: 5753-5758 (1996) of record) who teaches that when using the methods of Bonadio, organized bone repair is achieved"... since Bonadio's method leads to organized bone formation, what would lead the skilled artisan to any conclusion other than the reasonable expectation that he combined teachings of Ahrens, Bonadio and Lee would have led to organized functional bone repair?"

Applicants assert however, that:

1) Fang describes use of BMP-4 and not BMP-2.
2) Fang specifically notes that fibroblasts express the BMP-4, following direct gene transfer at the site!

Fang describes a cell type presumptive of being an osteoblast also at the site, and not expressing the BMP, but responding to expressed BMP from the fibroblast! Thus Fang supports Applicants contention that Bonadio serves exclusively to highlight contributions of paracrine effects on bone formation, i.e., gene transfer to differentiated cells, which secrete the BMP, in a limited fashion can promote osteoblast recruitment and some bone formation at the site, and shows that Bonadio's direct gene transfer experiments do not specifically target uptake by stem or progenitor cells. Again, Applicants maintain that the CHO-expressing BMP cells, in this context, serve as a control for the teachings of Bonadio, i.e. a cell at the site, which expresses the BMP, and enables paracrine effects of BMP at a site of bone infirmity.

Applicants maintain that paracrine effects of BMP-2 are not sufficient to promote organized bone formation and prevent bone resorption at the site of a bone infirmity. Applicants demonstrate this in Example 11, and have provided Declarations to this effect that better bone formation occurs the BMP is expressed predominantly by the MSCs as this provides for autocrine and paracrine effects, which yields better, qualitative and quantitative bone formation, which is organized along the defect edges, and subject to no appreciable resorption.

In addition, the Examiner has also rejected claim 27 in view of the above cited references, further in view of Wozney, under 35 USC 103.

Wozney describes expression of a BMP receptor for BMP-2 in cells responding to the growth factor. Applicants maintain, that since Bonadio, Ahrens and Lee fail to describe the use of ex-vivo cultured MSC transduced/transformed with BMP-2 **alone**, in inducing organized functional bone formation at a site of bone infirmity, as described above, then the engineering of such cells to further express a BMP receptor is not rendered obvious, in consideration of Wozney.

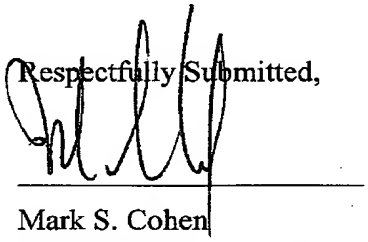
Similarly, the Examiner's rejection of claim 28 in view of the above cited references, further in view of Hattersley, under 35 USC 103 is traversed. Hattersley describes the use of PTH and its receptor in the context of BMP-2. Applicants maintain, that since Bonadio, Ahrens and Lee do not render obvious the methods of inducing functional bone formation via implanting **only** ex-vivo cultured MSC transfected/transduced with BMP-2 are not obvious in view of the art, neither is the MSC expression of a PTH/PTH receptor. Therefore, Applicants submit that the additional reference does not render the instant invention obvious.

Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of the claims under 35 U.S.C. 103.

Accordingly, Applicants submit that the pending claims are allowable, and that Applicants have addressed all prior Rejections. Their favorable reconsideration and allowance is respectfully requested. Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below.

Should any fee be due, the undersigned Attorney hereby authorizes the United States Patent and Trademark Office to charge Deposit Account No. 50-3355 for any fees required.

Respectfully Submitted,



Mark S. Cohen
Registration No. 42,425
Attorney for Applicants

Date: January 18, 2006

Pearl Cohen Zedek Latzer, LLP
Rockefeller Plaza, Suite 1001
New York, NY 10020
Telephone: 212 632 3494
Facsimile: 212 632 3490